Initial Statistical Plan

Seema Sonnad, PhD –
Center for Clinical Epidemiology and Biostatistics

Outcomes will be compared between groups using T-tests or Mann-Whitney tests for continuous variables and Chi-squared or Fischers exact tests for dichotomous variables. Spearmans rank correlation will be used to assess associations between continuous variables. Logistic regression analysis will be used to identify risk factors for the development of vasopressin deficiency. Receiver operating characteristic curves will be used to assess accuracy of initial copeptin, vasopressin, arterial base deficit and lactate values in predicting the need for transfusion and development of vasopressin deficiency.

Dr. Sonnad passed away mid-trial and the final statistics were performed by Ms Zimmerman and Dr. Mascha

Final Statistical Plan:

Nicole Zimmerman, MS and Edward Mascha, PhD
Cleveland Clinic, Section of Biostatistics, Quantitative Health Science and Outcomes Research

Methods

Blinded analysis was performed with groups being assigned as A and B. Unblinding of groups was done after statistical analysis.

Patients were summarized on demographics and pre-enrollment clinical characteristics by randomized groups using appropriate summary statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%)). Balance between randomized groups on baseline characteristics was assessed using absolute standardized difference (ASD), defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation. Any characteristic with ASD > $1.96 \times \sqrt{\frac{1}{n_A} + \frac{1}{n_B}}$ was considered imbalanced between groups, where n_A and n_B correspond to the number of patients in groups A and B respectively.[1] Resuscitation variables, study drug administration, and vasopressor use were summarized by group using appropriate summary statistics.

Primary and secondary analyses were intent-to-treat, including all randomized patients. Patients who died within 48 hours were assigned the worst observed outcome in the study population. For example, patients who died within 48 hours were assigned the highest quantity of 48-hour blood products administered as observed in our study population.

Primary Analysis

We estimated the effect of A on the total amount of 48-hour blood products used using the two-sample Wilcoxon rank sum test and Hodges-Lehmann estimation of location shift. This nonparametric approach is appropriate because the total amount of blood products used exhibited a right skewed distribution that did not normalize after a log transformation.

Secondary Analyses

A was compared to B on volume of vasopressors and crystalloids used within 48 hours after enrollment using the two-sample Wilcoxon rank sum test and Hodges-Lehmann estimation of location shift. The effects of A on acute respiratory distress syndrome (ARDS), renal failure, death in the OR, and overall mortality were assessed using separate logistic regression models using a log link to estimate relative risk. The A effects on time to abdomen closure, time to ventilator removal, ICU length of stay, and hospital length of stay were estimated as hazard ratios from separate Cox proportional hazard regression models.

Continuing Review

Basic Info

Confirmation Number:	**cfcgfigj**
Protocol Number:	**811293**
Created By:	**SIMS, CARRIE**
Principal Investigator:	**SIMS, CARRIE**
Protocol Title:	**Arginine Vasopressin during the Early Resuscitation of Traumatic Shock**
Short Title:	**AVERT Shock Trial**
Protocol Description:	**Massive resuscitation in trauma is associated with a relative vasopressin deficiency. This study will investigate the impact of early vasopressin supplementation during resuscitation and evaluate copeptin as a biomarker. Trauma patients who receive more than 6 units of blood product within 12 hours of arrival will be randomized to receive vasopressin infusion or placebo for 48 hours. Serial blood samples will be taken for 5 days post-injury. Clinical and demographic data will be recorded.**
Submission Type:	**Biomedical Research**
Application Type:	**FULL**

PennERA Protocol Status

Completed

Level of IRB Review Required

Expedited Review

The following documents are currently attached to this item:

There are no documents attached for this item.

Summary of protocol modifications approved since last continuing review
Please provide a description of changes which have been reviewed and approved by the IRB since the last continuing review.

Subject Enrollment

Target subject enrollment at Penn

0

Target enrollment at other centers (multi-center study)

0

Number of subjects enrolled at Penn since the study was initiated

0

Actual enrollment at participating centers

0

Number of subjects enrolled at Penn since the last continuing review

Total number of subjects who provided consent

0

Number of subjects determined to be ineligible

0

Number of subjects currently active/on study

0

Number of subjects lost to follow-up

0

Number of subjects no longer participating for other reasons

0

Number of subjects who have completed the study

0

Number of subjects who have withdrawn from the study

0

Race:

American Indian or Alaskan Native

0

Asian

0

Black or African American

0

Native Hawaiian or Pacific Islander

0

White

0

Other

0

Unknown or Not Reported

0

Ethnicity:

Hispanic or Latino

0

Not Hispanic or Latino

0

Gender

Male

0

Female

0

Other

0

Unknown / Not Reported

0

Total

0

Vulnerable Populations

Has your study enrolled pregnant woman?*

No

Has your study enrolled prisoners?*

No

Has your study enrolled children?*

No

Subject Withdrawal

How many subject voluntarily withdrew from the study?

0

How many subjects were withdrawn from the study at the request of the PI/Co-PI?

0

Number of subjects withdrawn due to adverse events/unanticipated problems

0

Subject withdraw reason*
If subjects voluntarily withdrew or were withdrawn, please indicate the reasons.

Issues with recruitment/retention, informed consent, or other issues
If applicable, please provide a brief summary of any difficulty you experienced obtaining/retaining subjects or obtaining informed consent during the entire approval period. Additionally, please indicate if there have been any complaints about the research.

Informed Consent Process*
Recognizing that informed consent encompasses much more than a form or document there are a number of methods employed to educate a potential subject as to what is involved in a particular research project. The forms used are one method for documenting the informed consent process.Is written informed consent required for this project?
No

Is written HIPAA authorization required?*

No

New Findings

Significant preliminary observations/interim findings
Have there been any significant preliminary observations/interim findings during the past approval period. If yes, please describe below.

DMC or DSMB exists*
Does a data monitoring committee (DMC) or data and safety monitoring board (DSMB) exist?
No

DMC or DMB Report Status

The following documents are currently attached to this item:

There are no documents attached for this item.

Multi-site trial summary
If this study is a multi-site trial, provide a narrative summary of any relevant reports that have been received in the past year, regardless of whether the report has been previously submitted to the IRB.

Disclosure of Significant Financial Interests*
Investigators (persons responsible for the design, conduct or reporting of this research protocol) must disclose any of the following financial interests / relationships with any entity that sponsors, provides support, or otherwise has a financial interest in the conduct or outcome of this research protocol (Outside Organization): Payments received for the past 12 months from a publicly traded Outside Organization for personal services (e.g., consulting, lecturing / speaking, service on the Scientific Advisory Board) plus the value of any current equity that when aggregated exceeds $5,000Payments received for the past 12 months from a non-publicly traded Outside Organization for personal services that in total exceed $5,000, or having any equity interestMembership on the governing board of any Outside Organization, including service on its board of directors, or having a position of authority or responsibility to act in its best interests, including being an officer, manager, partner, or limited liability company member with management responsibilityInvestigators must also disclose any financial interest in a drug, device or other product or a competing product (IP rights), regardless of whether the IP has been patented, licensed, or assigned to the Penn, if such IP is being tested, evaluated, or developed in, or if its commercial value could be affected by, this protocol.Investigators are not required to disclose equity in mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles.Does any Investigator (or his or her spouse or dependent children) have a SIGNIFICANT FINANCIAL INTEREST, as defined above?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials and the Financial Disclosure Policy for Research and Sponsored Projects with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Study Completion / Expiration

Study Complete*
Is this study complete?
No

Study Complete - Explanation
If study is completePlease indicate why (eg., research related activities and data analysis are complete, required number of subjects reached, issues with protocol safety,etc.)

The following documents are currently attached to this item:

There are no documents attached for this item.

IRB Approval Expired*
Has IRB approval for this protocol expired or will it expire before the scheduled IRB review?
No

Research During IRB Approval Lapse
If the IRB approval for the protocol has expired or will expire before the scheduled IRB review, confirm that no research related activities occurred/will occur without approval from the IRB unless the PI contacted the Office of Regulatory Affairs and the IRB Executive Chair (or authorized designee) determined that it is in the best interest of subjects to continue during the lapse in IRB approval. For example, in a clinical trial there are (1) subjects who are enrolled but not on intervention, (2) subjects who are on intervention, and (3) subjects who have completed the intervention phase and are in follow up. The IRB Executive Chair must evaluate each of these groups separately regarding continuation of participation in the research after IRB approval has expired.Have any research activities occurred, or will any research activities need to occur, during the lapse in IRB approval?
No

Unanticipated Problems*
Since the last IRB Review, have there been any unanticipated study related events that have not been previously reported to the IRB?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Adverse Events*
Since the last IRB review, has the profile of adverse events (in terms of frequency, severity, or specificity) changed from previous experience or as documented in the research protocol, informed consent document, or investigator's brochure?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Documents attached from the IRB protocol application.

The following documents are currently attached to this item:

There are no documents attached for this item.

List of Documents Details
Please detail the rationale for why any of the above documents are not attached to the submission (i.e. No Investigator's Brochure, Protocol, or Consent Forms are utilized for this protocol).

Protocol Details

Resubmission*
No

Study Personnel

Principal Investigator

Name:	**SIMS, CARRIE**
Dept / School / Div:	**4507 - SU-Trauma**
Campus Address Mail Code	**6070**
Address:	**Room 5035 Traumatology & Surg** **5 Maloney 3400 Spruce Street**
City State Zip:	**Philadelphia PA 19104-6070**
Phone:	**215-588-5154**
Fax:	**-**
Pager:	
Email:	**carrie.sims@uphs.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**10/17/2014**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

Name:	**STEELE, JOY**
Dept / School / Div:	**4502 - SU-Surgery Administration**
Campus Address Mail Code	**6070**
Address:	**3400 Spruce Street** **2 Dulles**
City State Zip:	**Philadelphia PA 19104-6070**
Phone:	**-**
Fax:	**-**
Pager:	
Email:	**Joy.Steele@uphs.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/21/2018**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**RODRIGUEZ, MYRA**
Dept / School / Div:	**2100 - Health System**
Campus Address Mail Code	
Address:	**Clinical Practices of U of P** **Surgery Admin COO**
City State Zip:	
Phone:	**-**
Fax:	**-**
Pager:	
Email:	**myra.rodriguez@uphs.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**01/19/2017**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Other Investigator

None

Responsible Org (Department/School/Division):

4507 - SU-Trauma

Key Study Personnel

None

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?

Investigator Initiated Trial*
Is this an investigator initiated trial?
Yes

If Yes, please be aware that the investigator may be required to create and manage a record of this trial in https://clinicaltrials.gov.

Drugs or Devices*
Does this research study involve Drugs or Devices?
Yes: Drugs or products administered to subjects not indicated in the FDA -approved drug labeling

IND Exemption

No

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below
110,134

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://somapps.med.upenn.edu/pennmanual/secure/pm/investigational-product-management Please check the box Yes if you have reviewed the guidance.
No

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
IDS will be used to receive, store or dispense the drug, herbal product or other chemical entity

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
No

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
Yes

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
No

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
No

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
Yes

Primary Focus*
Clinical Trial (prospectively assigning subjects to health-related interventions to evaluate outcomes)

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
x	**Drug**
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
	Diagnostic test/procedure (research-related diagnostic test or procedure)
x	**Obtaining human tissue for basic research or biospecimen bank**
x	**Survey instrument**
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Department budget code

None

Multi-Site Research

Other Sites

No other sites

Management of Information for Multi-Center Research

The following documents are currently attached to this item:

There are no documents attached for this item.

Protocol

Abstract
Trauma patients who are transfused with mutiple blood products to treat shock frequently develop inappropriately low vasopressin levels. Vasopressin is a hormone necessary to maintain an adequate blood pressure and low levels are associated with the need for increased transfusions, vasopressors and additional morbidity. Vasopressin is routinely used in the ICU to treat septic shock and other disease processes resulting in decreased vasopressin levels and low blood pressure. This study will investigate the potential benefit of early vasopressin supplementation during the resuscitation of trauma patients and the applicability of using copeptin as a vasopressin biomarker. Trauma patients who receive 6 or more units of blood product within 12 hours of arrival will be randomized to receive a vasopressin bolus plus infusion or a similar volume of a placebo (normal saline) for 48 hours. Serial blood samples will be taken for 5 days post-injury. Clinical and demographic data will be recorded prospectively.

Objectives

Overall objectives
1) To identify risk factors that predict the development of vasopressin deficiency in trauma patients. 2) To determine the clinical benefit of early vasopressin supplementation during the resuscitation of trauma patients. 3) Evaluate the clinical applicability of using copeptin, a stable chaperone molecule, as a biomarker for the development and resolution of vasopressin deficiency in trauma patients.

Primary outcome variable(s)
1. number of blood products transfused within 48 hours post injury

Secondary outcome variable(s)

1) need for vasopressors within 48 hours post injury 2) resuscitation related complications with in 30 days post injury a. intra-abdominal hypertension b. open abdomen free days c. ventilator-free days d. ICU-free days e. development of ARDS 3) development of renal failure 4) development of mutiple organ failure 5) volume of crystalloid requirement within 48 hours post injury 6) mortality

Background

Trauma remains the leading cause of death for those under the age of 40 in the United States, with a large percentage of patients dying from hemorrhagic shock within the initial post-injury hours (1-3). Although resuscitation with intravenous fluids and blood products has remained the gold standard over the last twenty years, vigorous volume resuscitation may not be curative and has been associated with the development of serious complications including coagulopathy, acute lung injury, and abdominal compartment syndrome (4-7). Massive resuscitation also profoundly alters the neuroendocrine milieu needed to maintain vasomotor tone and these severely injured patients may progress to a state of recalcitrant hypotension, multi-organ failure, and ultimately death (8-13). The inclusion of vasoactive hormones during resuscitation could potentially prevent the profound hypotension seen in late stage shock, limit the need for aggressive volume and blood product resuscitation, and decrease the incidence of resuscitation-associated complications. As such, there exists an urgent need to evaluate novel resuscitation strategies that target neuroendocrine deficiencies in hemorrhagic shock. The hormone arginine vasopressin (AVP), in particular, may prove a useful adjunct during resuscitation. Secreted by the posterior pituitary, vasopressin is essential for maintaining vasomotor tone during hemorrhagic shock and low levels are associated with the development of catecholamine-resistant hypotension and profound venodilation (14-16). Trauma patients who require more than 5 units of blood products during their initial resuscitation are at risk for developing a vasopressin deficiency, the need for vasopressor support, and longer ICU requirements.(10,16) Vasopressin has enjoyed widespread off-label use as a vasopressor in cardiac arrest, septic shock, and post-cardiopulmonary vasodilatory shock.(17-27) Although high dose vasopressin supplementation has been shown to improve blood pressure, decrease blood loss and improve survival in animal models of lethal hemorrhage, clinical studies investigating the use of exogenous vasopressin during hemorrhagic shock are limited to case reports and one small randomized control trial investigating the use of low dose vasopressin during the resuscitation of trauma victims.(28-34) A European multi-center, randomized control trial investigating the use of high dose vasopressin in pre-hospital trauma patients with refractory hemorrhagic shock is currently planned, but has not begun patient enrollment at this time.(35) Our central hypothesis is that trauma patients who present in hemorrhagic shock are at risk for vasopressin deficiency and would benefit from early vasopressin supplementation. The proposed study builds on our strong observational data demonstrating the development of a vasopressin deficiency in critically ill trauma patients and is supported by our preliminary laboratory data demonstrating improved hemodynamics and mitochondrial function following resuscitation with vasopressin in an animal model of decompensated shock. We hypothesize that the early use of vasopressin during the resuscitation of traumatic shock will result in fewer blood transfusions, a decreased need for crystalloid resuscitation, and a lower incidence of resuscitation-related complications. Cited References: (1) CDC. Deaths: final data for 2006. Available at http://www.cdc.gov/nchs/nvss/new_mortality.htm. (2) Peng R, Chang C, Gilmore D, Bongard F. Epidemiology of immediate and early trauma deaths at an urban level 1 trauma center. Am Surg. 1998;64:950-954. (3) Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg. 2004;198:20-26. (4) American College of Surgeons. Advanced Trauma Life Support® (Student Manual, 7th edition). American College of Surgeons 2004. (5) Revell M, Greaves I, Porter K. Endpoints for fluid resuscitation in hemorrhagic shock. J Trauma. 2003;54:S63-67. (6) Sterns SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful? Current Opinion in Crit Care. 2001;7:422-430. (7) Cotton BA, Guy JS, Morris Jr. JA, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26:115-121. (8) Sims C, Jaffe R, Foreman J, Menger R, Sonnad S, Pascual J, Sarani B. Adrenal insufficiency in hemorrhagic shock. Crit Care Med 2008;36:A65 (9) Strong ML, Grill EK, Sims CA. Altered thyroid function in exsanguinating trauma patients. Crit Care Med 2008;36:A65. (10) Sims CA, Holmes L, Jaffe R, et al. Vasopressin supplementation : the missing link of trauma exsanguination protocols? J Trauma (submitted) (11) Rush BF Jr. Irreversibility in the post-transfusion phase of hemorrhagic shock. Adv Exp Med Biol. 1971;23:215-234. (12) Thiemermann C, Szabo C, Mitchell A, Vane JR. Vascular hyporeactivity to vasoconstrictor agents and hemodynamic decompensation in hemorrhagic shock is mediated by nitric oxide. Proc Natl Acad Sci USA 1993;90:267-271. (13) Pietzman AM, Billiar TR, Harbrecht BG, et al. Hemorrhagic shock. Curr Prob Surg 1995;32:925-1002. (14) Altura BM. Evidence that endogenous vasopressin plays a protective role

in circulatory shock. Role for reticuloendothelial system using Brattlebro rats. Experientia 1908;36:1080-1082. (15) Errington ML, Rocha e Silva M Jr. Vasopressin clearance and secretion during haemorrhage in normal dogs and in dogs with experimental diabetes insipidus. J Physiol 1972;227:395-418. (16) Sims CA, Holmes L, Jaffe R, et al. Relative vasopressin deficiency in hemorrhagic shock: Are initial biomarkers predictive? J Trauma (submitted) (17) Lindner K, Dirks B, Strohmenger H, et al. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997;349:535-537. (18) American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. III. Adult basic life support. Circulation 2000;102(suppl 8):I22-59. (19) Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105-13. (20) Dellinger RP, Levy MM, Cartlet JM, et al. Surviving sepsis campaign: international guidelines for the management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327. (21) Holmes C, Walley K, Chittock D, Lehman T, Russell J. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Int Care Med 2001;27:1416-21. (22) Malay M, Ashton R, Landry D, Townsend R. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999;47:699-704. (23) Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122-1125 (24) Dunser MW, Mayr AJ, Stallinger A, et al. Cardiac performance during vasopressin infusion in postcardiotomy shock. Int Care Med 2002;28:746-51. (25) Masetti P, Murphy SF, Kouchoukos NT. Vasopressin therapy for vasoplegic syndrome following cardiopulmonary bypass. J Cardiac Surg 2002;17:485-9. (26) Morales DL, Garrido MJ, Madigan JD, et al. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Ann Thoracic Surg 2003;75:926-30. (27) Papadopoulos G, Sintou E, Siminelakis S, et al. Perioperative infusion of low-dose of vasopressin for prevention and management of vasodilatory vasoplegic syndrome in patients undergoing coronary artery bypass grafting a double-blind randomized study. J Cardiothorac Surg 2010;5:17. (28) Stadlbauer KH, Wagner-Berger HG, Raedler C, et al. Vasopressin, but not fluid resuscitation, enhances survival in a liver model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Anesthesiology. 2003;98:699-704. (29) Voelckel WG, Raedler C, Wenzel V, et al. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. Crit Care Med. 2003;31:1160-1165. (30) Haas T, Voelckel WG, Wiedermann F, et al. Successful resuscitation of a traumatic cardiac arrest victim in hemorrhagic shock with vasopressin: a case report and brief review of the literature. J Trauma 2004;57:177-9. (31) Sharma RM, Setlur R. Vasopressin in hemorrhagic shock. Anesth Analg 2005;101;833-4. (32) Tsuneyoshi I, Onomoto M, Yonetani A, et al. Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. J Anesth 2005;19:170-3. (33) Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation 1999;100:226-229. (34) Cohn SM, McCarthy J, Stewart RM, Jonas RB, Dent DL, Michalek JE. Impact of low dose vasopressin on trauma outcome: prospective randomized pilot study. 5th Annual Academic Surgical Congress, Feb. 3, 2010. (35) www.vitris.at accessed Sept 23, 2010.

Study Design

Phase*
Phase II

Design
This a randomized, double blinded, placebo controlled study. Injured patients requiring 6 or more units of blood product within 12 hours of their initial trauma evaluation will be randomized to receive either vasopressin (bolus of 4 units + 0.04 units/min) or placebo (normal saline at equal volume) for 48 hours. The vasopressin or placebo infusion will be weaned as tolerated to maintain a mean arterial blood pressure of 65 mmHg for 48 hours. The Investigation Drug Service at the Hospital of the University of Pennsylvania will coordinate randomization using computer assigned 6 block assignment stratification. Pharmacy will prepare blinded study bolus/infusions of vasopressin and normal saline. Drug bolus syringes and infusion bags will be labeled with a randomization code. The IDS pharmacist delivers the study drug to the trauma bay to store in the trauma bay pharmacy refrigerator in a bin labeled AVERT Shock. The randomization number, delivery and expiration date is acknowledged by the PI and/or study coordinator. The study drug is retrieved when the trauma exsanguination protocol is activated and/or at the request of the PI, research coordinator or research assistant. If a patient meets criteria, the PI is

notified and the study drug is prepared for enrollment. Study medication may be prepared by trauma bay staff, anesthesia residents, ICU staff, the research nurse or PI. A dispensing card is included with each kit. AVERT Shock Study Randomization Number: 1XX Patient MR#_____ Call Dr. Carrie Sims at 215-588-5154 immediately after mixing study medication! Instructions: 1. Attach needle to syringe containing undiluted vasopressin/ placebo (with purple label) 2. Add entire contents of syringe to 250mL normal saline IV bag, mix gently and label with infusion sticker 3. Attach needle to 10mL syringe for BOLUS dose 4. Withdraw 10mL from the IV bag and label with bolus sticker 5. Keep this card for study coordinator or place in trauma bin on door to storage room 6. Medication should be administered ONLY AFTER speaking with Dr. Sims and AFTER 6th unit of blood product. Date Made:_____Time Made:_____ M a d e by:_____ Print Initial The order and randomization number is entered in Sunrise or Emtrac. Pharmacy is notified of the enrollment and the Day 2 bag of study medication is requested. Patients who remain hypotensive in the intensive care unit following surgical control of bleeding will be resuscitated in a standard way practiced by the HUP trauma/surgical critical care team and at the discretion of the treating physicians. Hypotensive patients (MAP less than 65 mmHg) will be resuscitated with isotonic crystalloid solution to a goal CVP of 8-10 mmHg and with blood products as needed to correct anemia (hemoglobin =10 g/ dL) and coagulopathy (INR 1.4). Following appropriate volume resuscitation, if the patient remains hypotensive with a MAP less than 65, norepinephrine will be utilized. If the norepinephrine requirement exceeded 20 mcg/min, epinephrine will be added as a second agent. Patients enrolled in this study will not be eligible for off-label use of vasopressin. Serial blood samples will be taken for 5 days post-injury. Clinical and demographic data will be collected on case report forms (CRFs) for 30 days post enrollment. Research staff enter clinical information directly on the CRF in real time. CRFs are primary source documents as the research staff is present for key time points during the active 5 day study window. We hypothesize that the use of vasopressin will result in fewer transfusions and less morbidity.

Study duration

Subjects will actively participate in the study for a total of 5 days. Clinical data regarding their hospitalization and outcome will be collected throughout their hospitalization for up to 30 days. The following variables will be recorded for all enrolled subjects: demographic data (age, gender, mechanism, specific injuries, injury severity score, Glasgow coma score, past medcial history), outcome data (length of ventilatory support, ICU length of stay, hospital lengthy of stay, discharge destination, mortality), general daily laboratory values drawn for standard patient care (complete blood count, chemistry panel, albumin, arterial blood gas, lactate, coagulation parameters, liver function tests), the amount of crystalloid used in the first 48 hours, the amount and type of blood product transfused at 48 hours and at 30 days, the development of multi-organ failure within 30 days, and all complications as defined and reported to the Pennsylvania Trauma Outcome Study. Subjects will receive a vasopressin or placebo bolus plus infusion for 48 hours. The vasopressin infusion/placebo will weaned to mainatian a mean arterial blood pressure of 65 mmHg. Serial blood samples will be obtained according to the following schedule: On enrollment and prior to initiation of vasopressin/placebo infusion and then serially every 8 hours for 48 hours, every 12 hours for 24 hours, then every 24 hours for 2 days. Retrospectively, blood samples taken for routine care on admission to the trauma bay, that would otherwise be discarded, will be assayed. All study blood samples will be assayed for for cortisol, cortisol binding globulin, vasopressin and copeptin. We anticipate enrolling 100 subjects (50 treatment and 50 placebo) over 3 years with completion and analysis of the data by 4 years. Community consultation will begin Nov 15, 2010 with an anticipated study start date of April 1, 2013.

Resources necessary for human research protection

Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.

Research staff will include a PI, research coordinator, and 1 to 2 research assistants. All research staff will be familiar with the study protocol and execution prior to initiation. The PI is a qualified trauma surgeons with clinical trial experience and training. The research coordinators will have clinical trial experience and will directly oversee the training of research assistants in order to coordinate the study

and ensure compliance. All research staff will have CITI training. After the enrollment of the first subject and again after the fifth, the study site will be reviewed by an independent monitor in order to ensure proper documentation, enrollment, and protocol adherance. This review process will be conducted again every 3-6 months depending on subject accrural. The entire research staff will conduct meetings every two weeks and the PI and research coordinator will meet at least weekly. Data Safety Monitor Board: This independant board will consists of 3-5 experts in the field of trauma with clinical trial experience as well as trained biostatitician with clinical trials training/experience. (Please see attached DSMB Charter). The DSMB will have no real or apparent conflict of interest and will not be under the supervision of the principal investigator or research staff. The DSMB will provide an independant evaluation of seriouas adverse events and unanticipated problems involving risk to subjects and report such findings to the IRB, National Trauma Institute (NTI), and the Human Research Protection Office (HRPO) of the DOD/U.S. Army Medical Research and Material Command (USARMC). As a condition of DOD research, the DSMB will promptly report discrepancies or problems to the IRB, NTI, and HRPO and has the authority to stop a research study in progress, remove individual subject volunteers, and take whatever steps necessary to protect the safety and well-being of research subjects unitl the IRB can assess the DSMB's report. Additionally, there will be an independent Medical Monitor who will be informed of all adverse events and deaths. He/She will inform the DSMB, IRB, and NTI as needed. He/She also has the authority to unenroll patients and convene an emergent DSMB meeting. Study Population: The Hospital of the University of Pennsylvania (HUP) evaluates approximately 2,500 trauma patients annually. HUP has an exsanguination protocol in place that allows for the rapid mobilization of resources, personnel, blood products, and medications to expeditiously treat injured patients. Utilization of the exsanguination protocol provides as an excellent mechanism for evaluating resuscitation techniques and strategies. Finally, the trauma division at HUP has a proven record of conducting multi-disciplinary trauma, critical care, and emergency research. All patients, including enrolled subjects, will be admitted to the trauma and surgical critical care service. They will be managed according to generally accepted medical standards for traumatic injury, which includes surgical interventions, damage control maneuvers, and sub-specialty consultation as needed and at the discretion of the treating trauma surgeon/surgical intensivist.

Characteristics of the Study Population

Target population
All injured trauma patients (18 years to 65 years old) who require 6 or more units of blood product to treat their injuries during the initial resuscitation period defined as the first 12 hours following their initial trauma evaluation. Patients will not be included or excluded based on racial, gender, or socio-economic status. That being said, the majority of the trauma patients who require large volume resuscitation at the Hospital of the University come from an urban environment and are primarily victims of penetrating injuries (gunshot woundings and stabbings; 67%). Based on our previous observational studies, approximately 80-85% of the patients who would qualify for this study were young African American males from communities that border HUP.

Subjects enrolled by Penn Researchers
100

Subjects enrolled by Collaborating Researchers
0

Accrual
Trauma patients admiited to the Hospital of the University of Pennsylvania (HUP) (throuqh February 3, 2015) who require 6 or more units of blood product within the initial 12 hours of resuscitation will be identified by the trauma surgeon, research coordinator and/or research assistant. HUP is a level 1 trauma center (approximately 2,500 contacts annually) with a trauma exsanguination protocol in place. This allows for the rapid mobilization of resources, personnel, blood products, and medications to expeditiously treat injured patients. We will utilize the exsanguination protocol to identify and enroll patients. Based on our preliminary data, 100 patients (50 treatment and 50 placebo subjects) would be needed in order to achieve 80% power to detect clinically signficant differences in the total 48 hour

blood product requirement at the 0.05 significance level. A blood product transfusion of 6 or more units was chosen because the amount of transfusion has been shown to correlate with severe complications and poor clinical outcome (1, 2, 3) Specifically, Moore et al noted that transfusion of 6 or more units of packed red blood cells was the strongest predictor for the development of multi-organ failure (OR =8.6) (4) Additionally, our observational work suggests that a transfusion requirement of more than 5 units of blood product is associated with the development of a vasopressin deficiency, increased ventilator days and increased ICU length of stay. Because the nature of exsanguination and resuscitation is time-critical in a population that cannot provide informed consent by virture of their shocked and compromised state, we will be seeking an exception from informed consent requirements [FDA 21 CRF 50.24] with community consultation (please see attached EFIC and community consultation plan). (1) Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg. 2002; 68: 566-572. (2) Offner PJ, Moore EE, Biffl WL, Johnson JL, Silliman CC. Increased rate of infection associated with transfusion of old blood after severe injury. Arch Surg 2002; 137: 711-716. (3) Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: A meta-analysis. Journal of Trauma, Injury Infection and Critical Care. 2003; 54: 908-914. (4) Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg. 1997; 132: 620-624. (5) Sims CA, Holmes L, Jaffe R, et al. Vasopressin supplementation : the missing link of trauma exsanguination protocols? J Trauma (submitted) The Trauma Center at Penn Medicine will transfer from its current base of operations at the Hospital of the University of Pennsylvania (HUP) to Penn Presbyterian Medical Center (PPMC). Effective February 4th 2015, PPMC will become Penn Medicines level-1 Regional Resource Trauma Center. The Pennsylvania Trauma Foundation will recognize the 25 year history of the Penn Trauma Program as the same program at the new location. As a result of the move, the AVERT Shock Research Trial will continue to recruit patients in traumatic shock in the same fashion but at the new location. It should also be noted that PENN Investigational Drug Service (IDS) will also continue to dispense kits without any changes in procedures- except out of the new location.

Key inclusion criteria
Trauma patients between the ages of 18 and 65 who require 6 or more units of blood product during their initial 12 hours of resuscitation will be considered for enrollment.

Key exclusion criteria
Patients with a history of steroid use within the last 3 months Patients with chronic renal insufficiency Patients with a traumatic brain injury requiring neurosurgical operative intervention or who have neurologic trauma deemed non-survivable will also be excluded. Patients with an active coronary syndrome, history of myocardial infarction or coronary artery disease will be excluded. Patients who are pregnant will be excluded. Patients less than 18 years old will be excluded. Patients who have opted out by bracelet identification or by listing themselves on the "Non-Participant" roster Patients under the jurisdiction of the department of corrections and considered prisoners prior to the initation of the research intervention will be excluded Patients who require an emergency room thoracotomy we will be excluded.

Vulnerable Populations

x **Children Form**

Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form

Fetuses and/or Neonates Form

x **Prisoners Form**

x **Other**

None of the above populations are included in the research study

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
Given the nature of trauma and the physiologic consequences associated with hemorrhagic shock, all

eligible trauma patients in this study would be considered cognitively or decisionally impaired. Because many severely injured patients require more than 6 units of blood product within 15 to 30 minutes of arrival and because of the emergent nature of the proposed research, obtaining informed consent from the patient or their surrogate may not be practicable in many circumstances. As such, we will be seeking an Exception from the Informed Consent Requirement (EFIC) for emergency research with community consultation (see attached appendix). Information regarding the study, as well as the potential risks and benefits, will be presented to the patient's next of kin or surrogate as soon as they are identified. HIPAA authorization and consent to continued participation will be obtained from the patient's next of kin or surrogate. Whenever possible, HIPAA authorization and consent will be obtained from the patient's next of kin PRIOR to enrollment. If the subject becomes capable of consenting within the 30 day study period, he/she will informed of the study including the risks and benefits. HIPAA authorization and consent will be obtained from the patient. If he/she declines, he/she will be de-enrolled. All data and blood samples except for that pertaining to safety will be purged. On occasion, enrolled patients may become arrested while in hospital. If consent for enrollment has been obtained prior to the arrest, the IRB will be consulted to determine if subjects can continue in the study. If the arrest (and not merely detainment or police presence) occurs prior to obtaining consent, the patient will be de-enrolled given the risk of undue influence or coercion.

Subject recruitment
Given the unexpected nature of trauma, subjects will not be recruited for this study a priori of their injury. Rather as part of our community consultation and study advertisement plan (see attached), potential patients will be made aware of this research and given the opportunity to "opt out" of participation. Patients who do not wish to participate will be encouraged to wear an "opt-out" bracelet and to list their names on the "Non-Participant" list. The study advertisement plan will include an internet web page describing the study with a powerpoint link, newspaper/radio ads and research brochures/flyers/posters available in the waiting areas of the emergency department, trauma clinic, and ICU. A trauma patient/family interview and focus group sessions will also be instrumental in our community consultation and outreach plan.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

As part of our community consultation plan, we will be offering a small financial compensation to subjects. Subjects who participate in the trauma patient/family semi-structured survey will be offered a candy bar as a small token. Focus group participants will be offered a $50 gift card to cover the costs of travel, parking, and child care in order to attend the focus group session. Light refreshments will be provided at each focus group session.

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
Patients who require 6 or more units of blood product during the first 12 hours of resuscitation will be randomized to receive either vasopressin (4 units bolus plus an infusion of 0.04 units/min) or placebo (normal saline). Patients may have an arterial line, central line, and/or swan ganz catheter placed at the discretion of the trauma attending as part of the subjects routine care. The vasopressin (or placebo) will be weaned as tolerated to maintain the mean arterial blood pressure of 65 mmHg for the next 48 hours. Patients who remain hypotensive in the intensive care unit following surgical control of bleeding will be resuscitated with isotonic crystalloid solution to a goal CVP of 8-10 mmHg and blood products needed to correct anemia (hemoglobin less than 10 g/dL) and coagulopathy (INR greater than 1.4) Following appropriate volume resuscitation, if the patient remains hypotensive with a MAP less than 65, norepinephrine will be utilized. If the norepinephrine requirement exceeded 20 mcg/min, epinephrine will be added as a second agent. This resuscitation guideline is currently practiced at the HUP Surgical Intensive Care Unit. Serial blood samples will be collected in the trauma bay (emergency room), pre-enrollment (prior to the study drug and then serially every 8 hours for 48 hours, every 12 hours for 24 hours, then every 24 hours for 2 days. Retrospectively, blood samples taken for routine care on admission to the trauma bay and that would otherwise be discarded, will be assayed. Study blood samples will be assayed for cortisol, cortisol binding globulin, vasopressin, platelet function and peripheral mononuclear cell function. Laboratory values sent for the routine care of the patient will be recorded for 30 days post enrollment. The Trauma Center at Penn Medicine will transfer from its current base of operations at the Hospital of the University of Pennsylvania (HUP) to Penn Presbyterian Medical Center (PPMC). Effective February 4th 2015, PPMC will become Penn Medicines level-1 Regional Resource Trauma Center. The Pennsylvania Trauma Foundation will recognize the 25 year history of the Penn Trauma Program as the same program at the new location. As a result of the move, the AVERT Shock Research Trial will continue to recruit patients in traumatic shock in the same fashion but at the new location. It should also be noted that PENN Investigational Drug Service (IDS) will also continue to dispense kits without any changes in procedures- except out of the new location.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

Analysis Plan
Outcomes will be compared between groups using T-tests or Mann-Whitney tests for continuous variables and Chi-squared or Fischers exact tests for dichotomous variables. Spearmans rank correlation will be used to assess associations between continuous variables. Logistic regression analysis will be used to identify risk factors for the development of vasopressin deficiency. Receiver operating characteristic curves will be used to assess accuracy of initial copeptin, vasopressin, arterial base deficit and lactate values in predicting the need for transfusion and development of vasopressin deficiency. Bland-Altman analysis will be used to assess agreement between vasopressin and copeptin levels. Serious Adverse Events (SAE's) and unanticipated problems will be reported within 5 days of the event to the University of Pennyslvanias IRB as well as to the PI and the Data and Safety Monitor for this project. Safety boundaries will be established a priori. Safety monitoring will be performed using a group sequential procedure with three interim analyses. These three interium analyses will occur when 25, 50, and 75 patients have been enrolled. The OBrien-Fleming stopping boundaries will be used. All statistical testing will be two-sided with a significance level of 5%. The test statistic will be the log-rank procedure, expressed as a normally distributed z-score. The statistic will be computed such that positive values indicate benefit to the treated group relative to the control group. The OBrien-Fleming stopping bounds at the first, second, and third interim analyses are 3.438, 2.431, and 1.985 [Piantadosi S. Clinical Trials. A Methodological Perspective. John Wiley, New York 1997, Table 10.2, page 248]. The interim

p-values corresponding to these stopping bounds are 0.0006, 0.0151, and 0.0471, respectively. For example, if the test statistic at the first interim analysis exceeds 3.438 then the group sequential procedure will have indicated that the null hypothesis is rejected and the study can be stopped. The DSMB will make final decision to stop or continue the trial based on the results of these interim analyses and other available information.The Data Safety Monitor will evaluate the evidence and deliver a recommendation addressing whether the enrollment of subjects should be put on hold for further evaluation of safety data. If there is no difference between treatment arms in the endpoints, the Data Safety Monitor will use the information as input to their recommendation of continuing the trial. The recommendations will be communicated to each institution's IRB as well as to the FDA. This information will be communicated to the IRB, NTI, and DOD.

The following documents are currently attached to this item:

There are no documents attached for this item.

Are you conducting research outside of the United States?
No

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

- x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**
- x **Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.**

Subject Confidentiality
Samples (without patient identifiers) will be labeled with the study number. Samples will be stored in a locked laboratory facility on Dulles 5. Samples will be stored for 5 years and then will be destroyed. The clinical laboratories at the Univeristy of Pennsylvania will provide laboratory reports to the Investigator (either directly or via the Medview and/or Sunrise computer system). The results will be stored at the investigative site as source data and used for source data verification of data written into the CRF. Consent, patient data and case report forms will be collected and stored in a locked cabinet. Data will be entered and stored on a password-protected computer in Dr. Sims' office. Only Dr. Sims and her research team (assistant and coordinator) will have password access to this computer. The office itself is locked with front door security code and a second locked office door. Each patient will be assigned a study number. A separate database will be used to link each patient to their assigned study number. Only the assigned study number will be directly connected to patient data. The database linking each patient to their assigned study number will be destroyed five years after the conclusion of the study. The data collected will only be used for the proposed IRB study. Representatives of the National Trauma Institute, US Army Medical Research and Material Command (USAMRMC) of the Department of Defense, and the Human Research Protection Office of the DOD/USAMRMC are authorized to review the research records at any time. As part of the community consultation process, trauma patients and their families will be interviewed and small focus groups will be conducted. No indentifying information will be collected during these interviews and participation will be entirely

voluntary (please see community consultation plan). The small focus groups will be conducted in a semi-structured manner and in the presence of an IRB member. These focus group meetings will be audiotaped, transcribed, and analyzed. Follwoing transcription, the audiotape will be destroyed. Appropriate measures will be enforced to protect the identity of patients in all presentations and publications as required by local/regional/national requirements.

Sensitive Research Information*

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

Subject Privacy

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Consents, patient notes, CRF's will be stored in a locked facility immediately accessible only to the research staff. Each patient will be assigned a study number. A separate database will be used to link each patient to their assigned study number. Only the assigned study number will be directly connected to patient data. The database linking each patient to their assigned study number will be destroyed at the conclusion of the study. Data will be entered and stored on a password-protected computer in Dr. Sims' office. Only Dr. Sims and her research team (assistant and coordinator) will have password access to this computer. The office itself is locked with front door security code and a second locked office door. Representatives of the National Trauma Institute, US Army Medical Research and Material Command (USAMRMC) of the Department of Defense, and the Human Research Protection Office of the DOD/ USAMRMC are authorized to review the research records at any time. The patient or surrogate will be approached by the PI, research coordinator or research assistant in a discrete and private manner after the trauma and/or surgical critical care team has had the opportunity to update the patient or surrogate regarding the patient's clinical condition. As part of the community consultation process, trauma patients and their familys will be interviewed and small focus groups will be conducted. No indentifying information will be collected during these interviews and participation will be entirely voluntary (please see community consultation plan). Patients and/or their family's will be approached prior to discharge from the hospital or in the trauma clinic during their follow up appointments. The PI, research coordinator or research assistant will contact patients and/or their families in a discrete and private manner. Participation will be entirely voluntary and the semi-structured interviews will be conducted in private at the patient's bedside or in the clinic examination rooms. The small focus groups will be arranged in advance with community organizations and will be conducted in a semi-structured manner. An IRB member will be invited to attend these meetings. These focus group meetings will be audiotaped, transcribed, and analyzed. Follwoing transcription, the audiotape will be destroyed.

Data Disclosure

Will the data be disclosed to anyone who is not listed under Personnel?

Data will disclosed to members of the research team, Data Safety Monitor Board, Office of Regulatory Affairs, Office of Human Research, and the FDA as needed. Additionally, the representatives of the National Trauma Institute, USARMC and DOD are authorized access to all research data.

Data Protection*

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- **Telephone and fax number**
- x **Electronic mail addresses**
- **Social security numbers**
- x **Medical record numbers**
- **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
Yes

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
Yes

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
Yes

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
Yes

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
Yes

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision

of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
not applicable

Consent

1. Consent Process

Overview
Given the unpredictability and emergent nature of trauma, we will not be able to identify potentially eligible patients until they arrive to the trauma bay. In all cases, these patients will be severely injured, hemodynamically unstable and unable to consent for themselves. Given the urgent need and the time-sensitive nature of the proposed research, we will be seeking an Exception from Informed Consent for Emergency Research (EFIC). EFIC can only be used in rare circumstances in which the patient presents in a life-threatening emergency and the proposed research presents a possibility for direct benefit to the patient, but consent to participate in the research is not possible. Additionally, such research can only be done when it is not known if the current treatments are clearly effective or beneficial. The requirements for conducting this type of research are delineated in the FDA guidelines (FDA 21 CRF 50.24) and include the following: Each requirement will be addressed individually. 1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo controlled investigations, is necessary to determine the safety and effectiveness of particular interventions. Trauma remains the leading cause of death for those under the age of 40 in the United States, with a large percentage of patients dying from hemorrhagic shock within the initial hours after a severe injury.[1-3] Although resuscitation with intravenous fluids and blood products has been the gold standard for the last twenty years, vigorous volume resuscitation may not be curative and has been associated with the development of serious complications including coagulopathy, acute lung injury, and abdominal compartment syndrome.[4-7] Massive resuscitation also profoundly alters the neuroendocrine milieu needed to maintain vasomotor tone and these severely injured patients may progress to a state of recalcitrant hypotension, multi-organ failure, and ultimately death.[8-13] The inclusion of vasoactive hormones during resuscitation could therefore potentially prevent the profound hypotension seen in late stage shock, limit the need for aggressive volume and blood product resuscitation, and decrease the incidence of resuscitation-associated complications. The hormone arginine vasopressin (AVP) may prove a useful adjunct during resuscitation. Secreted by the posterior pituitary in response to hypotension, vasopressin is essential for maintaining vasomotor tone during hemorrhagic shock and low levels are associated with the development of catecholamine-resistant hypotension and profound venodilation.[14,15] Clinically, low plasma vasopressin levels are associated with recalcitrant hypotension, increased transfusion requirements, and additional morbidity in trauma patients undergoing massive resuscitation.[10] While there are a few case reports demonstrating the beneficial effect of vasopressin in the resuscitation of hemorrhagic shock, vasopressin has been primarily investigated in several animal models as an adjunct during resuscitation[16-21]. In a porcine model of lethal hemorrhage, infusion of high dose vasopressin prior to surgical control was associated with improved blood pressure, decreased blood loss, and significantly improved survival when compared to fluid resuscitation alone.[17] Similarly, when compared to a more traditional vasopressor, such as epinephrine, in an uncontrolled hemorrhagic shock model in swine, high dose vasopressin was associated with improved overall survival.[16] Recently Cohn et al conducted the only reported double-blinded, randomized trial of vasopressin in trauma patients.[22] In this small pilot study, patients with acute traumatic injury presenting with a systolic blood pressure of less than 90 mmHg received either vasopressin (4 IU bolus + 0.04 units/min) or placebo within one hour. Treatment with either vasopressin or placebo was continued for the next 5 hours. Subjects were randomized using the exception from informed consent for emergency research [FDA 21 CRF 50.24]. Cohn et al demonstrated that low dose vasopressin infusion following traumatic injury decreased fluid requirements and restored vasopressin levels to more appropriate values. Importantly, vasopressin was not associated with increased adverse events, organ dysfunction or 30 day mortality. While this study is encouraging, further research is clearly needed to demonstrate definitive benefit. Clinically, injured patients who require aggressive resuscitation are at risk for vasopressin deficiency. In a prospective, observational study of trauma patients presenting with hemorrhagic shock, we found vasopressin levels precipitously declined despite

ongoing blood loss and the need for continued resuscitation. In patients who required more than 20 units of blood product prior to admission to the intensive care unit, vasopressin levels were markedly elevated on presentation to the trauma bay but fell significantly with each 5 units of blood product transfused. Trauma patients who developed inappropriately low vasopressin levels were more likely to need subsequent vasopressor support, more blood product transfusions and had longer ICU stays. [10,23] Supplementing vasopressin early in the resuscitation of hemorrhagic shock may prevent the development of a vasopressin deficiency and improve patient outcome. Our initial work, as well as available human and animal studies, suggests that the increase in vasomotor tone provided by vasopressin will be beneficial to trauma patients requiring 6 units of blood product within the initial 12 hours of hospital admission. The proposed double-blind, randomized, controlled study is designed to assess the safety and efficacy of low dose vasopressin given in conjunction with standard resuscitative strategies for 48 hours after randomization in hopes of improving clinical outcomes after severe traumatic shock. (2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; (ii) The intervention under investigation must be administered before consent from the subjects legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation. Unlike the majority of disease states, injured patients do not anticipate getting hurt and any person can be a victim of trauma without warning. The traumatic event (e.g. motor vehicle crash, fall, or gunshot wounding) is unpredictable, generally painful, and frequently requires rapid intervention in order to prevent the loss of life and decrease the risk of serious complications. The patients who would be eligible for the AVERT Shock trial will universally present to the hospital severely injured, in shock and unable to consent for themselves. Frequently, this group of severely hurt patients are rapidly intubated, aggressively resuscitated and brought to the operating room or the IR suite for hemorrhage control within minutes of their initial arrival. The resuscitative effort is well on the way by the time the patient's family is located - a process that typically takes hours to days. And, in fact, if the patient is not carrying identification, it is not unusual for the patient's identity may remain unknown for several hours to days. This study proposal will investigate the early administration of vasopressin and is intended to supplement the urgent resuscitation of these critical injured patients. The hormone vasopressin is essential for maintaining vasomotor tone during hemorrhagic shock and low levels are associated with the development of catecholamine-resistant hypotension and profound venodilation.[21,24,25] We have demonstrated that massive resuscitation (more than 5 units of blood product/12 hours) is associated with the development of a vasopressin deficiency. Inappropriately low levels of vasopressin in these patients are associated with the need for vasopressors, increased transfusion and volume requirements and additional morbidity. Currently there is no way to identify this deficiency in real-time and the assay for vasopressin is send-out laboratory test that takes at least 2 days to perform. Because many severely injured patients require more than 6 units of blood product within 15 to 30 minutes of arrival and because of the time-critical nature of the proposed research, obtaining informed consent from the patient or their surrogate prior to initiating the research protocol may not be practicable in most circumstances. This challenge was clearly demonstrated in a previous study investigating trauma resuscitation in which the proposed intervention had to be initiated within 30 minutes in patients presenting in hemorrhagic shock. Only 6% of the subjects in this study could be enrolled with prospective informed consent and 94% were enrolled using EFIC. Had the investigators been required to enroll only subjects able to provide informed consent, they may have been able to complete the study, but it would have substantially expanded the financial and human resources needed; and would have likely taken a decade to complete.[26] Although every effort will be made to contact the subjects legal representative or family member PRIOR to enrollment, we anticipate that obtaining informed consent from the majority of patients who would qualify for the AVERT Shock trial will not be feasible. (3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) Subjects are facing a life-threatening situation that necessitates intervention; (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. Participation in the AVERT Shock Trial holds the prospect of direct benefit to seriously injured patients requiring massive transfusion. Clinically, severely injured patients who require aggressive resuscitation to save their lives are at risk for vasopressin deficiency. In a prospective, observational study of trauma patients presenting with hemorrhagic shock, we found vasopressin levels precipitously declined despite ongoing blood loss and the need for continued resuscitation. Our preliminary clinical research has demonstrated

that trauma patients who present in hemorrhagic shock are at risk for developing a vasopressin deficiency with the subsequent need for vasopressor support, increased blood product transfusion and prolonged ICU care. In patients who required more than 20 units of blood product prior to admission to the intensive care unit, vasopressin levels were markedly elevated on admission to the trauma bay but fell significantly with each 5 units of blood product transfused.[10,23] These clinical observations are in agreement with animal studies demonstrating that prolonged shock leads to vasopressin deficiency and the development of catecholamine-resistant hypotension.[21,25,27] Vasopressin has been investigated as an adjunct in several animal models. In a model of lethal hemorrhage, infusion of high dose vasopressin prior to surgical control was associated with improved blood pressure, decreased blood loss, and significantly improved survival when compared to fluid resuscitation alone.[17] Similarly, when compared to a more traditional vasopressor, such as epinephrine, in an uncontrolled hemorrhagic shock model, high dose vasopressin was associated with improved overall survival.[16] There are multiple case reports describing the beneficial use of exogenous vasopressin for the treatment of hemorrhagic shock in severely injured patients. [18-21] The concept of using vasopressin at physiologic doses (i.e. low dose), however, was first suggested by Landry et al to treat the profound vasodilation observed in septic shock.[28] Interestingly, vasopressin given at low doses does not act as a pressor agent in normal volunteers or in patients suffering from shock states not associated with diminished vasopressin levels (e.g. cardiogenic shock). In patients with vasodilatory shock states where endogenous vasopressin is quite low, treatment with low dose vasopressin is extremely effective in improving blood pressure. When infused at 0.04 units/min, serum vasopressin levels increase to roughly 100 pg/dl - a concentration that would be appropriate in the setting of hypotension from a variety of causes.[29] At low doses, vasopressin is associated with improved hemodynamics in septic patients. Low dose vasopressin is frequently used as an adjunct in critical care settings to treat septic shock and its use as an adjunct is endorsed by the Surviving Sepsis Campaign.[30] Although there does not appear to be a significant mortality benefit overall, patients with less severe sepsis may fair better when treated with vasopressin and do not demonstrate an increase in adverse events. [31] Because trauma patients may also have low blood pressures despite aggressive resuscitation, individual clinicians, including those at the Hospital of the University of Pennsylvania, currently use vasopressin off-label to treat post-traumatic hypotension. A secondary data base analysis investigating the use of early vasopressors in trauma patients, however, suggested using vasopressors within the first 24 hours of injury was associated with an increased mortality. Interestingly, vasopressin was the only vasopressor not found to be statistically significant on logistic regression.[32] In a similar retrospective review of trauma patients requiring vasopressors within the first 72 hours of admission, Collier et al report a correlation between vasopressin use and increased mortality (adjusted odds ratio of 1.2, 95% CI 1.1-2.4, p=0.02). Given the retrospective nature of this study, the authors conclude that vasopressin use may be a marker for increased illness or it may play a casual role in adverse outcomes. [33] These authors noted that prospective trials were needed to delineate the potential impact of vasopressin. Cohn et al have conducted the only reported double-blinded, randomized pilot trial of low dose vasopressin in trauma patients.[22] Under the exception from informed consent for emergency research (FDA 21 CRF 50.24), trauma patients with a systolic blood pressure less than 90 mmHg were randomized to receive either vasopressin (4 IU bolus with 0.04 units/min X 5 hours infusion) or placebo. Although not appropriately powered to detect a mortality difference, this study demonstrated a trend toward improved survival in patients treated with vasopressin at 24 hours (13% vasopressin vs. 23% control) and at 5 days (13% vasopressin vs. 25% control). The group treated with vasopressin tended to require less resuscitative fluid, although again this pilot study lacked power to detect statistical significance. Importantly, adverse events and organ dysfunction were similar in both groups. Although resuscitation with intravenous fluids and blood products has been the gold standard for the last twenty years, vigorous volume resuscitation may not be curative and has been associated with a myriad of complications including hypothermia, coagulopathy, acute lung injury, and abdominal compartment syndrome.[4-7] Based on animal data and experience in the clinical arena, vasopressin supplementation may potentially benefit severely injured trauma patients by improving hemodynamics, decreasing blood product transfusions, decreasing intensive care requirements, and minimizing resuscitation-related complications. Low dose vasopressin has enjoyed a wide-spread off-label use in septic shock without significant complications. Additionally, when used in the early resuscitation of trauma patients, low dose vasopressin was not associated with an increased complication rate when compared to standard therapy. As such, we believe the risks associated vasopressin use in the AVERT Shock Trial are reasonable in relation to what is known about severe hemorrhagic shock, the risks and benefits of standard fluid resuscitation therapy. (4) The clinical investigation could not practicably be carried out without the waiver. As mentioned in the response to (2), trauma by its very nature is unpredictable, painful, and frequently requires rapid intervention in order prevent loss of life. A delay in resuscitation or surgical intervention invariably

increases the risk of serious complications. Trauma patients who would be eligible for the AVERT Shock Trial will universally present to the hospital severely injured, in shock and unable to consent for themselves. Frequently, this group of severely hurt patients are rapidly intubated, aggressively resuscitated and brought to the operating room or the IR suite for hemorrhage control within minutes of their initial arrival. It is not unusual for these patients to receive more than 6 units of blood product within 15 to 30 minutes of arrival. In general, the resuscitative effort is well on the way by the time the patient's family is located - a process that typically takes hours to days The administration of vasopressin in the AVERT Shock trial is time-sensitive. In order to have the most benefit, vasopressin supplementation should be given early in the course massive resuscitation in order to restore serum levels in deficient patients. We have demonstrated that the development of a vasopressin deficiency in trauma patients is directly correlated to the volume of blood product transfused. In patients who required more than 20 units of blood product prior to admission to the ICU, vasopressin levels abruptly fell after 5 units of blood product - a volume that is commonly given within the first 30 minutes of resuscitation in these acutely injured patients. Although, the majority of the patients in our study who developed a vasopressin deficiency received more than 5 units of blood product prior to admission to the ICU, patients may be at risk up to 12 hours post admission. As such the overwhelming majority of patients who would be eligible for the AVERT Shock trial would be enrolled in the study prior to ICU admission. Given the time-critical nature of the proposed research, obtaining informed consent from the patient or their surrogate prior to initiating the research protocol will not be practicable in most circumstances. This challenge was clearly demonstrated in a previous study investigating trauma resuscitation. In this study of hemorrhagic shock and the potential benefit of a blood substitute, the intervention had to be initiated within 30 minutes. Only 6% of the subjects in this study could be enrolled with prospective informed consent and 94% were enrolled using EFIC. Had the investigators been required to enroll only subjects able to provide informed consent, they may have been able to complete the study, but it would have substantially expanded the financial and human resources needed; and would have likely taken a decade to complete.[26] In the case of the AVERT Shock Trial, we anticipate that roughly 10% of the potential subjects could be enrolled prospectively given the 12 hour enrollment period. Approximately 90% of the potential subjects would receive more than 5 units of blood product during their acute resuscitation in the trauma bay, operating room, or interventional radiology suite. Requiring informed consent would exclude the group of patients most at risk for vasopressin deficiency and, therefore, most likely to benefit from hormonal supplementation. (5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review. We have demonstrated that trauma patients who undergo massive resuscitation are at risk for developing a vasopressin deficiency. Moreover, the development of this deficiency appears to be directly correlated to the volume of blood product transfused. In patients who required more than 20 units of blood product prior to admission to the ICU, vasopressin levels abruptly fell after 5 units of blood product despite an ongoing need for volume resuscitation and blood pressure support. Although, the majority of the patients in our study who developed a vasopressin deficiency received more than 5 units of blood product prior to admission to the ICU, patients may be at risk for developing a deficiency up to 12 hours post admission. [10,23] In a prospective randomized pilot study of vasopressin supplementation in hypotensive trauma patients, Cohn et al also report the development of low vasopressin levels following resuscitation in trauma patients. Although the volume of blood product was not reported, patients who did not receive vasopressin supplementation had markedly decreased vasopressin levels 5 hours post-admission (24 ± 18 pg/dl on admission vs. 7 ± 7 pg/dl 5 hours later). Supplementation with vasopressin at 0.04 units/min increased this value to 23 ± 19 pg/dl. [22] In order to have the most benefit, vasopressin supplementation should be given early in the course massive resuscitation in order to restore serum levels in trauma patients at risk for vasopressin deficiency. Given this time-critical nature, obtaining informed consent from the patient or their surrogate prior to initiating the research protocol may not be practicable in most circumstances. That being said, every effort will be made to contact a legally authorized representative for each subject prior to the transfusion of 6 units of blood product within the 12 hour enrollment window, if feasible, in order to ask the legally authorized representative or family member for consent rather than proceeding without consent. Patients will be identified via activation of the trauma exsanguination protocol and trauma bay screening. The AVERT Shock research team will work with trauma chaplain and the trauma team in order to identify the subjects legally authorized representative (LAR) and/or family members. The AVERT Shock research team will document

attempted contact of the subjects LAR and/or family every 15 to 30 minutes after activation of the trauma exsanguinations protocol (or after the 4th unit of blood product within 12 hours has been given if the exsanguination protocol has not been activated). If the patient has been enrolled under EFIC, the research team will continue attempting contact every 15 to 30 minutes. The LAR or family member will be informed of the enrollment and given the opportunity to continue participation or to terminate enrollment. Prior to its use, this notification log will be reviewed and approved by the IRB. The notification document will be kept with the subjects Consent Documents and available for review. (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subjects participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section. An informed consent document has been submitted and will be used in all situations where the subject or their legally authorized representative can consent to the proposed research PRIOR to enrollment. If the subject has been enrolled under EFIC, information regarding the study, as well as the potential risks and benefits, will be presented to the patient's legally authorized representative or family member as soon as they are identified. HIPAA authorization and consent to continued participation will be obtained from the patient's LAR or family member. If the surrogate declines, the patient will be un-enrolled and subject's participation will be terminated. If the patient becomes capable of informed consent within the 30 day study period, he/she will be informed of the study and the potential risks/benefits. HIPAA authorization and consent will be obtained from the patient at that time. If the patient declines, he/she will be un-enrolled and the subject's participation will be terminated. Only safety information and mortality data will be recorded for 30 days post injury. If the patient is enrolled and dies prior to notification of the LAR or family member, information about the clinical investigation will be provided to the subject's legally authorized representative or family member, if feasible. This will be documented in the notification log and made available to the IRB for review. 7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subjects family member who is not a legally authorized representative, and asking whether he or she objects to the subjects participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review. The AVERT Shock trial has addressed the additional subject protection requirements and further detail can be found in the attached community consultation plan. In brief: (i) Consultation with trauma patients and their families admitted to the Hospital of Pennsylvania will be performed using a semi-structured survey and interview. Additionally, focus groups will be conducted at community-centers, churches, and mosques in the West Philadelphia area. (ii) Public disclosure, specifically in the West Philadelphia area and surrounding Metro-Philadelphia, will be conducted using radio advertisements, notification in the local newspaper the Metro, the University of Pennsylvanias public relations web announcements, flyers/posters within the hospital and distributed at community events, and notification on the Trauma Divisions Research Web page. This disclosure will occur prior to initiating the study. (iii) On completion and analysis of the study, the focus groups will reconvene for a community discussion of the results. Additionally, the results will be made available to the Metro and radio for community announcements. Results will be made available to the HUP trauma community using flyers distributed to patients/families and posters displayed in the emergency department, surgical intensive care units and clinic waiting areas. In addition to having access to the research staff during the distribution of this literature, a website where comments/concerns can be sent will be made available. (iv) An independent data safety monitoring board will be established (See attached DSMB Charter). Members of this board include: Dr. Andrew Peitzman (University of Pittsburgh), Dr. Stephen Cohn (University of Texas Health Center at San Antonio), and Dr. Mitch Cohen (University of California, San Fancisco). Dr. Charles Branas (University of Pennsylvania) will provide statistical oversight. (v) All

efforts will be made to contact a legally authorized representative or family member prior to enrollment in the AVERT Shock trial please see #6 of this section. Citations: 1. CDC. Deaths: final data for 2006. Available at http://www.cdc.gov/nchs/nvss/new_mortality.htm. 2. Peng R, Chang C, Gilmore D, Bongard F. Epidemiology of immediate and early trauma deaths at an urban level 1 trauma center. Am Surg. 1998;64:950-954. 3. Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg. 2004;198:20-26. 4. American College of Surgeons. Advanced Trauma Life Support® (Student Manual, 7th edition). American College of Surgeons 2004. 5. Revell M, Greaves I, Porter K. Endpoints for fluid resuscitation in hemorrhagic shock. J Trauma. 2003;54:S63-67. 6. Sterns SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful? Current Opinion in Crit Care. 2001;7:422-430. 7. 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Children and Adolescents
On occasion, patients who are less than 18 years old are brought to the trauma bay following severe and life-threatening trauma. These patients appear physiologically mature and it may be difficult to ascertain their true age. In general, the resuscitatative effort is well on the way by the time the patient's family is located and his/her age is revealed. In these circumstances, the patient's care and resuscitative efforts are identifical to those patients who are greater than 18 years old. Following community consultation and approval from the IRB, it is likely these patients will be enrolled and randomized prior to confirmation of their age. Information regarding the study, as well as the potential risks and benefits, will be presented to the patient's next of kin or surrogate as soon as they are identified. HIPAA authorization and consent to continued participation will be obtained from the patients next of kin or surrogate. Whenever possible, HIPAA authorization and consent will be obtained from the patient's next of kin PRIOR to enrollment. If the surrogate declines, the patient will be un-enrolled and subject's participation will be terminated. If the patient becomes capable of informed consent within the 30 day study period, he/she will be informed of the study and the potential risks/benefits. Assent to HIPAA authorization and study participation will be obtained from the patient . If the patient's age is known to be less than 18 prior to study initiation, he will not be enrolled in this study.

Adult Subjects Not Competent to Give Consent
Given the unpredictability and emergent nature of trauma, we will not be albe to identify potentially eligible patients until they arrive to the trauma bay. In all cases, these patients will be severely injured, hemodynamically unstable and unable to consent for themselves. Frequently these patients are rapidly intubated, aggressively resuscitated and brought to the operating room or IR suite for hemorrhage control within minutes of initial arrival. In general, the resuscitative effort is well on the way by the time the patient's family is located - a process that typically takes hours to days. Because many severely injured patients require more than 6 units of blood product within 15 to 30 minutes of arrival and because of the time-critical nature of the proposed research, obtaining informed consent from the patient or their surrogate may not be practicable in most circumstances. As such, we will be seeking an Exception from Informed Consent (EFIC) Requirement for Emergency Research with community consultation (see attached appendix). Following community consultation and approval from the IRB, eligible patients will be enrolled and randomized. Information regarding the study, as well as the potential risks and benefits, will be presented to the patients next of kin or surrogate as soon as they are identified. HIPAA authorization and consent to continued participation will be obtained from the patients next of kin or surrogate. Whenever possible, HIPAA authorization and consent will be obtained from the patient's next of kin PRIOR to enrollment. If the surrogate declines, the patient will be un-enrolled and subject's participation will be terminated.If the patient becomes capable of informed consent within the 30 day study period, he/she will be informed of the study and the potential risks/benefits. HIPAA authorization and consent will be obtained from the patient . If the patient declines, he/she will be un-enrolled and the subject's participation will be terminated. Only safety information and mortality data will be recorded for 30 days post injury.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
Waiver or alteration of required elements of consent

Minimal Risk*
The potential risk of using vasopressin at physiologic supplemental doses during the active phase of resuscitation from life-threatening hemorrhage is unknown. Secreted by the posterior pituitary, vasopressin an essential hormone needed for maintaining vasomotor tone during hemorrhagic shock and low levels are associated with the development of catecholamine-resistant hypotension and profound venodilation (1,2,3) Low dose vasopressin (0.04 units/min or less) is frequently used to treat various forms of vasoplegic shock in the the critically ill (4). Interestingly, vasopressin at low doses does not act as a pressor agent in normal volunteers or in patients with shock states associated with normal or elevated vasopressin levels (e.g. cardiogenic shock) (5). Although there is the potential risk for decreased blood flow to the heart, kidney, and small intestine, the use of low dose vasopressin to treat septic shock was not associated with increased adverse complications when compared to norepinephrine in a large randomized prospective trial (6). Vasopressin supplementation has been shown to improve blood pressure, decrease blood loss and improve survival in animal models of lethal hemorrhage (7,8). Clinical studies investigating the use of exogenous vasopressin during hemorrhagic shock are limited, but show promising results in case reports(9,10,11,12,13). Vasopressin is currently on

the formulary at HUP and is commonly used to treat the hypotensive trauma patient both in the OR and in the ICU. It is therefore possible that if the potential subject were not enrolled, he/she may still receive this therapy during resuscitation as part of their "routine" trauma care. (1) Altura BM. Evidence that endogenous vasopressin plays a protective role in circulatory shock. Role for reticuloendothelial system using Brattlebro rats. Experientia 1908;36:1080-1082. (2) Errington ML, Rocha e Silva M Jr. Vasopressin clearance and secretion during haemorrhage in normal dogs and in dogs with experimental diabetes insipidus. J Physiol 1972;227:395-418. (3) Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation. 1999;100:226-229. (4) Oliver JA, Landry DW. Endogenous and exogenous vasopressin in shock. Curr Opin Crit Care. 2007;13:376-382. (5) Landry DW et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation. 1997;95:1122-1125. (6) Russel JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Eng J Med. 2008;358:877-87. (7) Stadlbauer KH, Wagner-Berger HG, Raedler C, et al. Vasopressin, but not fluid resuscitation, enhances survival in a liver model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Anesthesiology. 2003;98:699-704. (8) Voelckel WG, Raedler C, Wenzel V, et al. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. Crit Care Med. 2003;31:1160-1165. (9) Krismer AC, Wenzel V, Voelckel WG, et al. Employing vasopressin as an adjunct vasopressor in uncontrolled traumatic hemorrhagic shock: three cases and a brief analysis of the literature [in German] Anaesthesist 2005;54:220-4. (10) Haas T, Voelckel WG, Wiedermann F, et al. Successful of a traumatic cardiac arrest victim in hemorrhagic shock with vasopressin : a case report and brief review of the literature. J Trauma. 2004;57:177-9 (11) Sharma RM, Setlur R. Vasopressin in hemorrhagic shock. Anesth Analg 2005;101:833-4. (12) Tsuneyoshi I, Onomoto M, Yonetani A, et al. Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. J Anesth 2005;19:170-3. (13) Stadlbauer KH, Wenzel V, Krismer AC, et al. Vasopressin during uncontrolled hemorrhagic shock: Less bleeding below the diaphragm, more perfusion above. Anesth Analg 2005;101:830-2

Impact on Subject Rights and Welfare*

This study will attempt to protect the patients rights by (1) informing the community and encorporating the community's concerns/comments into the final trial design and implementation, (2) providing an "opt out" option that will allow potential subjects to declare their wishes not to participate in the event of an injury (attached EFIC appendix), (3) informing and consenting the patient or surrogate prior to randomization whenever practicable (4) informing and obtaining consent for continued participation when a surrogate is identifed and (5) informing and consenting the patient when he/she regains capacity to make an informed choice. If consent is not obtained, the subject will be un-enrolled. Subjects enrolled will be cared for by the trauma and surgical critical care team who will be blinded to the treatment assignment. At anytime the attending surgeon and/or critical care provider may un-enroll the patient from the study and the treatment assignment will be unblinded. Patients enrolled in this study cannot be prescribed vasopressin during the first 5 days post injury. Because a variety of pressors are used to treat post injury hypotension this prohibition is not outside the realm of standard ICU practice. Furthermore, because vasopressin is available at HUP to treat post traumatic hypotension, it is possible that if the potential subject were not enrolled, he/she may still receive vasopressin during resuscitation as part of their "routine" trauma care.

Waiver Essential to Research*

Trauma remains the leading cause of death for those under the age of 40 in the United States, with a large percentage of patients dying from hemorrhagic shock within the initial post-injury hours (1,2,3). Potential therapeutic interventions will have the most impact if used early in the resuscitation, ultimately decreasing the morbidity and mortality associated with trauma. Given the unpredictability and emergent nature of trauma, potentially eligible patients cannot be identified prior to their arrival to the trauma bay. Moreover, patients who are severely injured and hemodynamically unstable are unable to consent for themselves. Frequently, these patients are rapidly intubated, aggressively resuscitated with blood products and brought to the operating room or IR suite for hemorrhage control within minutes of initial arrival. In general, the resuscitative effort is well on the way by the time the patient's family is located - a process that typically takes hours to days. Because many severely injured patients require more than 6 units of blood product within 15 to 30 minutes of arrival and because of the time-critical nature of the proposed research, obtaining informed consent from the patient or their surrogate may not be practicable in most circumstances. Please see an indepth discussion regarding EFIC for this study in the consent process section. (1) CDC. Deaths: final data for 2006. Available at http://

www.cdc.gov/nchs/nvss/new_mortality.htm. (2) Peng R, Chang C, Gilmore D, Bongard F. Epidemiology of immediate and early trauma deaths at an urban level 1 trauma center. Am Surg. 1998;64:950-954. (3) Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg. 2004;198:20-26.

Additional Information to Subjects
Contact information from the patient and/or the surrogate will be kept in a separate file that is not associated with any HIPPA or study data. Whenever appropriate, the subjects will be provided by mail or email additional pertinent information regarding safety, efficacy, and study results after participation. Participants will have the option of receiving a copy of the accepted manuscript reporting the study and its results.

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
Theoretically, the use of vasopressin may result in hyponatremia as well as decrease blood flow to the heart, kidneys, and small intestines. When given to healthy adults at low doses, however, low dose vasopressin does not act as a pressor and does not increase blood pressure (1). Moreover, when compared to norepinephrine (another frequently used vasopressor), vasopressin was not associated with more adverse events when used to treat septic shock (2). A secondary data base analysis investigating the use of early vasopressors in trauma resuscitation suggests that using vasopressors within the first 24 hours of injury is associated with an increased mortality. Interestingly, vasopressin was the only pressor not found to be statistically signficant on logistic regression but did have a hazard ratio of 1.7 (CI not reported, but crossed 0) (3). Because this study was a secondary analysis of data base, the dose and duration of vasopressin were not recorded. Moreover, the association between vasopressor use and mortality may not be a causal one. Recently Cohn et al conducted a pilot study investigating the use of low dose vasopressin in hypotensive trauma patients.(4) Under the exception from informed consent for emergency research (FDA 21 CRF 50.24), trauma patients with a systolic blood pressure 90 mmHg were randomized to receive either vasopressin (4 IU bolus with 0.04 units/min X 5 hours infusion) or placebo. Although not appropriately powered to detect a mortality difference, this study demonstrated a trend toward improved survival in patients treated with vasopressin at 24 hours (13% vasopressin vs. 23% control) and at 5 days (13% vasopressin vs. 25% control). Importantly, adverse events and organ dysfunction were similar in both groups. In the proposed study, subjects enrolled in the vasopressin arm will have the infusion started at 0.04 units/min after 6 units of blood product are administered. This infusion dose is standardly used at the HUP to treat septic and cardiogenic shock (4). This dose of vasopressin is also used "off-label" to treat post traumatic shock at the discretion of the trauma/ICU attending at HUP. Because the infusion in the proposed study will be weaned to a target mean arterial blood pressure of 65 mmHg and does not provide blood pressure support in otherwise healthy volunteers, it is anticipated the risks of using vasopressin will be minimized. Subjects who are not randomized to the vasopressin arm will receive a similar volume of normal saline which will also be weaned to a mean arterial blood presure of 65 mmHg. In the intensive care unit, patients who are hypotensive wil be resuscitated using a standardized protocol. Although vasopressin is aproved as a peripheral infusion, there is a risk of peripheral vasoconstricition and skin necrosis. As such, this medication will preferentially be given via central venous access. Patients who would qualify for this study routinely have central access placed for resuscitation and monitoring as part of their routine trauma care. Patients who have chronic renal insufficiency may be at increased risk for further renal dysfunction if enrolled in the study arm. (1) Landry DW et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation. 1997;95:1122-1125. (2) Russel JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Eng J Med.

2008;358:877-87. (3) Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. J Trauma 2008;64:9-14. (4) Cohn SM, McCarthy J, Stewart RM, Jonas RB, Dent DL, Michalek JE. Impact of low dose vasopressin on trauma outcome: prospective randomized pilot study. 5th Annual Academic Surgical Congress, Feb. 3, 2010. (5)http://www.crlonline.com/crlsql/servlet/crlonline

Potential Study Benefits

There are laboratory studies and clinical case reports suggesting that vasopressin provides hemodynamic stabilization in hemorrhagic shock and may be life-saving (1-7). Our observational data suggest that trauma patients who require more than 5 units of blood products during their initial resuscitation are at risk for developing a vasopressin deficiency and the need for vasopressor support. These patients also require more aggressive blood and crystalloid resusciatation and have more polonged ICU stays (8). Using vasopressin early in the resuscitative effort may prevent the profound hypotension seen in late stage shock, limit the need for aggressive volume and blood product resuscitation, improve mortality, and decrease the incidence of resuscitation-associated complications. Patients who are enrolled, but who receive the normal saline placebo rather than the vasopressin, will also be montitored aggressively with their blood pressure targeted to a MAP of 65 mmHg. Theoretically, this increased attention to to blood pressure in the placebo group may translate to improved care and earlier recognition of under-resuscitation or other complications. The information gained from this study has potential to change the way trauma patients are routinely resuscitated and may decrease the mortality and morbidity associated with hemorrhagic shock. (1) Stadlbauer KH, Wagner-Berger HG, Raedler C, et al. Vasopressin, but not fluid resuscitation, enhances survival in a liver model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Anesthesiology. 2003;98:699-704. (2) Voelckel WG, Raedler C, Wenzel V, et al. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. Crit Care Med. 2003;31:1160-1165. (3) Krismer AC, Wenzel V, Voelckel WG, et al. Employing vasopressin as an adjunct vasopressor in uncontrolled traumatic hemorrhagic shock: three cases and a brief analysis of the literature [in German] Anaesthesist 2005;54:220-4. (4) Haas T, Voelckel WG, Wiedermann F, et al. Successful of a traumatic cardiac arrest victim in hemorrhagic shock with vasopressin : a case report and brief review of the literature. J Trauma. 2004;57:177-9 (5) Sharma RM, Setlur R. Vasopressin in hemorrhagic shock. Anesth Analg 2005;101:833-4. (6) Tsuneyoshi I, Onomoto M, Yonetani A, et al. Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. J Anesth 2005;19:170-3. (7) Stadlbauer KH, Wenzel V, Krismer AC, et al. Vasopressin during uncontrolled hemorrhagic shock: Less bleeding below the diaphragm, more perfusion above. Anesth Analg 2005;101:830-2. (8) Sims CA, Holmes L, Jaffe R, et al. Vasopressin supplementation : the missing link of trauma exsanguination protocols? J Trauma (submitted)

Alternatives to Participation (optional)

Patients who elect not to participate in the proposed study will be managed according to accepted medical and trauma standards. Because vasopressin is an available therapeutic option at HUP, it is possible that patients who elect not to participate in the study will still receive a vasopressin infusion at the discretion of the treating anesthesiologist, trauma surgeon or critical care provider.

Data and Safety Monitoring

This study will be monitored by the Principle Investigator, the co-investigator, the clinical research assistant, the Sponsor/Contract research organization (National Trauma Institute/Department of Defense) and a Data and Safety Monitor Board. Consents, patient notes, CRF's will be stored in a locked facility readily accessible only to the research staff. Each patient will be assigned a study number. A separate database will be used to link each patient to their assigned study number. Only the assigned study number will be directly connected to patient data. The database linking each patient to their assigned study number will be destroyed at the 3 years following the conclusion of the study. Data will be entered and stored on a password-protected computer in Dr. Sims' office. Only Dr. Sims and her research team (assistant and coordinator) will have password access to this computer. The office itself is locked with front door security. An independent monitor will visit the research site within seven working days of randomization of the first and fifth patient . All subsequent monitoring visits will occur approximately every 3 months or as needed based upon the frequency of patient enrollment. The purpose of these visits is to ensure that the CRFs are completed correctly, the protocol is adhered to, to monitor drug accountability, and to discuss enrollment. The monitor will have direct access to source documents (original documents, data and records). All data, including the following items, must be

source data verifiable in source documentation other than the CRF: Existence of patient (initials, date of birth) Confirmation of participation in the trial (patient ID, trial ID, signed/dated informed consent form) Diagnosis/indication under investigation Adverse events or signs and symptoms (description and duration) Relevant medical history and/or concomitant illness and concomitant medications Reason for exclusion or withdrawal Serious adverse events (SAEs), mortality, and patient status will be followed through Day 30. All adverse events will be reported to an independent medical monitor. Serious Adverse Events (SAE's) and unanticipated problems will be reported within 5 days of the event to the institution's IRB as well as to the Lead Investigator (Dr. Carrie Sims, University of Pennsylvania),the Data and Safety Monitor for this project, and the National Trauma Institute. Safety boundaries will be established a priori using the methods described in Bolland and Whitehead. The Data Safety Monitor will evaluate the evidence and deliver a recommendation addressing whether the enrollment of subjects should be put on hold for further evaluation of safety data. If there is no difference between treatment arms in the endpoints, the Data Safety Monitor will use the information as input to their recommendation of continuing the trial. The recommendations will be communicated to each institution's IRB as well as to the FDA. Three interium analysis are planned based on patient enrollment and will be conducted after the 25th, 50th, and 75th patient enrolled.. At a minimum, the DSMB will meet to review safety data every 3-6 months. Again the Data and Safety Monitor will evaluate the data and deliver a recommendation addressing whether the enrollment of subjects should continue. This information will be communicated to each institution's IRB.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
The risk benefit ratio in this study is favorable. The vasopressin infusion will be started at a rate found to be safe in other shock states and will be weaned as the subject's hypotension is reversed. Moreover, low dose vasopressin was not associated with increased mortality or other adverse events when compared to norepinephrine in patients with septic shock. Because patients who require more than 5 units of blood products during their initial resuscitation are at risk for developing a vasopressin deficiency, using vasopressin early in the resuscitative effort may prevent the profound hypotension seen in late stage shock, limit the need for aggressive volume and blood product resuscitation, decrease the incidence of resuscitation-associated complications, and decrease mortality.

General Attachments

The following documents are currently attached to this item:

There are no documents attached for this item.

Patients who died before the event were assigned a censoring time equal to the longest observed time to event.

Other study outcomes including Total SOFA score, Day 5 IO balance, and complications were summarized by study groups using appropriate summary statistics.

Sensitivity Analyses

As a sensitivity analysis, we performed a per-protocol analysis, including only patients who survived for 48 hours after enrollment and thus reached endpoints of interest.

We used a significance criterion of 0.05 for each primary and secondary analysis. Analyses were performed using R version 3.3.2 (R Project for Statistical Computing, Vienna, Austria).